

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
17 January 2002 (17.01.2002)

PCT

(10) International Publication Number  
**WO 02/04024 A1**

(51) International Patent Classification<sup>7</sup>: **A61K 45/06**,  
38/28, 31/64, 31/44, 31/425, 33/24, A61P 3/10

(21) International Application Number: **PCT/CA00/01152**

(22) International Filing Date:  
29 September 2000 (29.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
09/608,272 30 June 2000 (30.06.2000) US

(71) Applicant and

(72) Inventor: **RIEVELEY, Robert, B.** [CA/CA]; 4102  
Yuculta Crescent, Vancouver, British Columbia V6N 3R5  
(CA).

(74) Agents: **OYEN, Gerald, O., S. et al.**; Oyen Wiggs Green  
& Mutala, #480 - The Station, 601 West Cordova Street,  
Vancouver, British Columbia V6B 1G1 (CA).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,  
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,  
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,  
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,  
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,  
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,  
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: COMPOSITION FOR THE TREATMENT OF DIABETES

(57) Abstract: This invention is directed to a novel method and composition for the treatment of diabetes mellitus (Type I, Impaired Glucose Tolerance ["IGT"] and Type II). More specifically, this invention pertains to a novel method and composition for orally treating diabetes mellitus by administering to a person afflicted with diabetes mellitus one or more insulin sensitizer chemicals, which increase the cells ability to utilize glucose, together with one or more orally ingested medications for the treatment of diabetes mellitus. A method for the treatment of diabetes mellitus comprising administering to a person with diabetes mellitus a therapeutic amount of an insulin sensitizer with a therapeutic amount of an anti-diabetic agent.



**WO 02/04024 A1**

COMPOSITION FOR THE  
TREATMENT OF DIABETES

TECHNICAL FIELD OF THE INVENTION

5

This invention is directed to a novel method and composition for the treatment of diabetes mellitus. More specifically, this invention pertains to a novel method and composition for orally treating diabetes mellitus (Type I, Impaired Glucose Tolerance ["IGT"] and Type II) by administering to a person afflicted with  
10 diabetes mellitus one or more insulin sensitizer chemicals, which increase the cells ability to utilize glucose, together with one or more orally ingested medications for the treatment of diabetes mellitus.

BACKGROUND OF THE INVENTION

15

It is estimated that 1.5 to 2% of the entire population of the world suffers from diabetes mellitus of some type. This includes Type I, Impaired Glucose Tolerance [IGT] and Type II. Of the fourteen million Americans with diabetes, roughly 90% have Type II (non-insulin-dependent) and roughly 10% have  
20 Type I (insulin-dependent) disease. Traditionally, diabetics have been doomed to suffer from chronic complications, including retinopathy, neuropathy, and nephropathy. However, in recent years, it has been found that by rigorously managing blood sugar levels, diabetics could substantially minimize long-term complications. The difficulty is to select a specific program for a specific diabetic,  
25 and have the diabetic faithfully follow the program. The American Diabetes Association now recognizes that there can be no universal guidelines. Rather, it recommends that dietary regimens and weight goals be tailored for each diabetic. This requires both greater commitment on the part of diabetics themselves, and greater involvement of medical professionals, particularly dieticians.

30

Diabetes mellitus is a chemical disorder of the human body primarily involving an inability of the body to properly utilize sugar and other chemical compounds in the metabolism of the body. It is characterized by an elevation in the concentration of sugar in the blood and also by the appearance of sugar in the urine.  
35 Specifically, diabetes mellitus is a metabolic disease in which carbohydrate utilization is reduced and that of lipid and protein enhanced; it is caused by an absolute or relative deficiency of insulin and is characterized, in more severe cases, by chronic hyperglycemia, glycosuria, water and electrolyte loss, ketoacidosis, and coma; long-term complications include development of neuropathy, retinopathy,

- 2 -

nephropathy, generalized degenerative changes in large and small blood vessels, and increased susceptibility to infection.

In general terms, diabetes mellitus is classified into three types, namely, Type I, IGT and Type II. In Type I diabetes, the beta cells in the pancreas, probably through an auto-immune reaction, cease producing insulin into the bloodstream of the person. Insulin is a polypeptide hormone, secreted by beta cells in the islets of Langerhans, that promotes glucose utilization, protein synthesis, and the formation and storage of neutral lipids. Obtained from various animals and available in a variety of preparations, insulin is used parenterally in the treatment of diabetes mellitus. Insulin is vitally important to the person because it enables the person to properly utilize and consume sugar in the bloodstream as part of the metabolism process.

In Type I cases, where the pancreas has ceased producing insulin, it is necessary for the afflicted person to inject insulin directly into the bloodstream at prescribed periodic intervals and dosages in order to control the level of sugar in the blood. This is called intravenous injection. Oral ingestion of insulin is also possible but usually less effective due to the degradation of insulin caused by the passage through the stomach and upper intestine.

In IGT and Type II diabetes, the beta cells of the pancreas continue to produce insulin but, some or all of the insulin may fail to bind to the body's cell receptors and/or internalization or uptake of insulin in the cells is reduced. In such Type II cases, there may be a sufficient level of insulin in the blood, but the ability of the cells to uptake glucose is reduced or non-existent because of reduced internalized insulin.

The existence of Type I, IGT or Type II diabetes in a person is usually determined by an oral glucose tolerance test (OGTT). OGTT is a test in which the fasting patient is orally given a known amount of glucose (sugar), and the blood is tested at intervals thereafter to note the quantity of sugar in the blood. A curve is then constructed from which important glycaemic information about the person can be drawn. The glucose tolerance test curve will typically show whether the patient is hyperglycaemic (diabetic) or whether the patient has too little sugar in his or her blood and is therefore hypoglycaemic.

- 3 -

Symptoms of hyperglycaemia (too much sugar) can be headaches, increased urination, thirst, nausea, weight loss, fatigue and coma. Hyperglycaemia can be caused by Hypoinsulinism, a condition in which the insulin producing beta cells of the pancreas fail to manufacture insulin or manufacture and secrete a  
5 reduced amount of insulin into the bloodstream. In such cases, levels of sugar in the blood are dramatically increased.

Hyperglycaemia can also be caused by failure of some or all of the available insulin in the blood to bind to the body's cell receptors and/or  
10 internalization of insulin in the cells is reduced.

Hypoglycaemia (too little sugar) is also a blood condition that diabetics must constantly guard against. The symptoms of hypoglycaemia are abrupt episodes of intense hunger, trembling of the hands and body, faintness, black  
15 spots before the eyes, mental confusion, sweating, abnormal behaviour, and, in severe cases, convulsions with loss of consciousness. In such cases, examination of the blood at the time of these attacks will show an extremely low level of circulating sugar in the blood.

20 Hypoglycaemia can be caused by Hyperinsulinism, a condition in which the insulin producing beta cells of the pancreas manufacture and secrete an excessive amount of insulin into the bloodstream. Levels of sugar in the blood are therefore dramatically reduced.

25 Transfer of glucose from the blood stream to the body cells is believed to be enabled by the binding of insulin to the cell receptors. Receptor bound insulin then increases the amount of insulin that is internalized in the cell. Internalized insulin results in increased utilization of glucose in the cell and consequently increased metabolism.

30 A drug that sensitizes the surface of a body cell to increase the cell's internalization or uptake of insulin, or is believed or purported to function by sensitizing the cell to insulin, is known and defined in the context of this description as an "insulin sensitizer".

35 The following is a list of drugs that have been or are being tested as insulin sensitizers:

1. BRL-49653 as produced by SmithKline Beecham or by some other advocate, and otherwise known as Rosiglitazone Maleate or by the trademark Avandia.
2. Pioglitazone HCL as produced by Takeda or some other advocate or supplier, also known as Actos.
3. Troglitazone, Noscal or Resiline as produced by Sankyo, Glaxo Wellcome or Warner-Lambert.
4. MC 555 as produced by Mitsubishi or some other advocate or supplier.
5. ALRT 268 as produced by Ligand or some other advocate or supplier.
6. LGD 1069 as produced by Ligand or some other advocate or supplier.
7. Chromic Picolinate, available commercially.
8. Diab II<sup>TM</sup> (otherwise known as V-411) or Glucanin and produced by Biotech Holdings Ltd. or Volque Pharmaceutical.
9. Vanadyl Sulfate, available commercially.
10. Chromic Polynicotinate, available commercially.
11. Metformin or Glucophage.

Intravenous injection is the anathema of all Type I and II diabetics forced to inject insulin. These diabetics today are cursed to a lifelong ritual of having to inject insulin into their bloodstream, usually several times a day, in order to keep the level of insulin in the blood within prescribed levels.

Considerable research is being conducted to develop an insulin which can be orally ingested and effective for the treatment of Type I or II diabetes. Such an effective orally ingestible insulin would be welcomed by Type I and Type II diabetics because it would no longer be necessary for them to undergo a daily routine of intravenous insulin injections. Unfortunately, to date, an effective orally ingested insulin has not yet been successfully developed.

A major hurdle is that stomach acids and gut enzymes of the person destroy most of the orally ingested insulin and hence the amount of ingested insulin that reaches the bloodstream is less than what is therapeutically required for the diabetic to function normally. Time release systems are being researched in an effort to alleviate this problem. The theory of these time release systems is to

incorporate the insulin with appropriate time release mechanisms so the insulin is not released until after the time release-insulin combination has passed through the digestive acids in the stomach and the preliminary stages of the digestive process.

5                   The following U.S. patents are relevant to the art of orally administered insulin:

- |    |           |   |   |
|----|-----------|---|---|
| 10 | 4,362,719 | - | Therapeutic Method and Compositions for the Treatment of Juvenile Diabetes Mellitus |
|    | 4,579,730 | - | Pharmaceutical Compositions Containing Insulin                                      |
|    | 4,602,043 | - | Treatment for Hypoglycemia  |
| 15 | 4,696,815 | - | Anti-Diabetic Pharmaceutical Forms and the Preparation Thereof                      |
|    | 4,708,868 | - | Anti-Diabetic Pharmaceutical Forms and the Preparation Thereof                      |
| 20 | 4,826,684 | - | Composition for, and Method of, Treatment of Diabetes                               |
|    | 4,849,405 | - | Oral Insulin and a Method of Making the Same  |
| 25 | 4,871,739 | - | Substituted 6H-7,8-dihydrothiapyrano (3,2-D)-pyrimidines as Hypoglycemic Agents     |
|    | 4,873,080 | - | Oral Anti-Diabetic Pharmaceutical Compositions and the Preparation Thereof          |
| 30 | 4,963,526 | - | Oral Insulin and a Method of Making the Same  |
|    | 4,978,667 | - | Substituted 6H-7,8-dihydrothiapyrano (3,2-d)-pyrimidines as Hypoglycemic Agents     |
| 35 | 5,057,517 | - | Piperazinyl Derivatives of Purines and Isosteres Thereof as Hypoglycemic Agents     |
|    | 5,187,154 | - | Diagnosis and Treatment of Humans with Diabetes or at Risk to Develop Diabetes      |
|    | 5,206,219 | - | Oral Compositions of Proteinaceous Medicaments                                      |
| 45 | 5,234,906 | - | Hyperglycemic Compositions  |
|    | 5,284,845 | - | Use of Oral Diazoxide for the Treatment of Disorders in Glucose Metabolism          |
| 50 | 5,380,526 | - | Antidiabetic Agent and Method of Treating Diabetes                                  |

- 5,422,125 - Method and Composition for Treatment of Insulin Resistance Syndromes
- 5 5,424,406 - Dihydrochalcone Derivatives which are Hypoglycemic Agents
- 5,444,086 - Naphthalenylmethyl Thiophenones as Antihyperglycemic Agents
- 10 5,468,755 - Therapeutic Process for the Treatment of the Pathologies of Type II Diabetes
- 15 5,478,852 - Use of Thiazolidinedione Derivatives and Related Antihyperglycemic Agents in the Treatment of Impaired Glucose Tolerance in Order to Prevent or Delay the Onset of Noninsulin-Dependent Diabetes Mellitus
- 20 5,510,360 - Azolidinediones as Antihyperglycemic Agents
- 5,532,256 - New Azolidinediones and Thiadiazolidinediones as Antihyperglycemic Agents
- 25 5,589,183 - Method and Apparatus for Treatment of Neurogenic Diabetes Mellitus, and Other Conditions
- 5,595,763 - Tungsten (VI) Compositions for the Oral Treatment of Diabetes Mellitus

30 IGT and Type II Diabetes can in certain cases be treated with one or more classes of drugs generally known as hypoglycaemics to reduce blood glucose levels.

One class of hypoglycaemics are known as "sulfonylureas". Trade-  
 35 marks for commercially available sulfonylureas include Glucotrol, Diabinese, DiaBeta, Micronase, Tolinase and Orinase. Sulfonylureas appear to stimulate the pancreas and increase the production of insulin from the beta cells in the pancreas. Unfortunately, there are potential unfavourable side effects from the use of sulfonylureas. Therefore, the less a patient is required to use a sulfonylurea, the  
 40 fewer side effects are likely to be experienced by that patient.

Another class of hypoglycaemics are known as "biguanides". Trade-  
 marks for some commercially available biguanides include Metformin and Glucophage. The physiological action of biguanides is not completely understood.  
 45 However, biguanides may divert glucose before reaching the blood stream thereby reducing blood glucose levels. Biguanides may also increase cell receptor

sensitivity. There are potential unfavourable side effects from the use of biguanides by a patient so the less a patient uses a biguanide, the less likely the patient is to experience unfavourable side effects.

5           A further class of hypoglycaemics is known as the "alpha-glucosidase inhibitors". Trade-marks for some alpha-glucosidase inhibitors include Precose, Prandase, and Acrabose. These drugs are believed to bind glucose in the gastrointestinal tract thereby reducing glucose absorption. Because there are unfavourable side effects associated with the use of alpha-glucosidase inhibitors, the  
10   less a patient uses such drugs, the less the patient is likely to experience unfavourable side effects.

### SUMMARY OF INVENTION

15           The invention is directed to a method and composition for the treatment of diabetes mellitus including Type I, IGT and Type II diabetes mellitus. More specifically, this invention pertains to a novel method and composition for treating diabetes mellitus by incorporating together a therapeutic amount of one or more insulin sensitizers along with one or more of an orally ingested insulin, an  
20   injected insulin, a sulfonylurea, a biguanide or an alpha-glucosidase inhibitor. A therapeutic amount of insulin sensitizer can comprise one microgram to 10 grams of one or more insulin sensitizers combined or used with one or more of:

a.       A therapeutically effective amount of an orally ingestible insulin which  
25       withstands degradation by passage through the stomach and upper intestine of the mammal so that a therapeutically effective level of insulin reaches the bloodstream of the mammal. The addition of the insulin sensitizer is to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the orally  
30       ingested insulin required for a therapeutic dose, and/or,

b.       An injected insulin product. The addition of the insulin sensitizer is to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the  
35       therapeutic dose required of injected insulin, and/or,



c. A sulfonylurea. The addition of the insulin sensitizer is to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the required therapeutic dose of the sulfonylurea hypoglycaemic, and/or,

d. A biguanide. The addition of the insulin sensitizer is to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the required therapeutic dose of the biguanide hypoglycaemic, and/or,

e. A alpha-glucosidase inhibitor. The addition of the insulin sensitizer is to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the required therapeutic dose of the alpha-glucosidase inhibitor hypoglycaemic.

The invention is directed to a method for the treatment of diabetes mellitus comprising administering to a person with diabetes mellitus a therapeutic amount of an insulin sensitizer with a therapeutic amount of an anti-diabetic agent.

The method can comprise an insulin sensitizer and an orally ingestible insulin or an insulin sensitizer and an injectible insulin. The method can include a pharmaceutical carrier with the therapeutically effective amount of the anti-diabetic agent and the insulin sensitizer. The anti-diabetic agent can be one or more substances selected from the group consisting of: (a) an orally ingestible insulin; (b) an injectible insulin; (c) a sulfonylurea; (d) a biguanide; or (e) an alpha-glucosidase inhibitor.

The invention is also directed to a composition for the treatment of diabetes mellitus in a mammal comprising: (a) a therapeutic amount of an insulin sensitizer; and (b) a therapeutic amount of an anti-diabetic agent. In the composition according to the invention, (a) the therapeutically effective amount of anti-diabetic agent can be an orally ingestible insulin which can be formulated to withstand degradation by passage through the stomach and upper intestine of the mammal so that a therapeutically effective level of insulin reaches the bloodstream of the mammal; and (b) the therapeutically effective amount of the insulin sensitizer can be one or more of an orally ingestible insulin sensitizer which can withstand degradation by the stomach contents and upper intestinal tract of the mammal and

can reach the bloodstream of the mammal and thereby sensitize the cells of the mammal to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the orally ingested insulin required for a therapeutic dose.

5           The therapeutically effective amount of anti-diabetic agent can be an injected insulin; and the therapeutically effective amount of insulin sensitizer can be one or more insulin sensitizers to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus  
10       reducing the therapeutic dose required of injected insulin. The composition can include a pharmaceutically acceptable carrier. The insulin can be synthetic insulin. The orally ingestible insulin can be present in the composition in the range of about 1 mcg to 100 mg and the insulin sensitizer can be present in the composition in the range of about 10 mcg to 10 mg. The injected insulin can be present in the  
15       composition in the range of about 1 mcg to 100 mg and the insulin sensitizer can be present in the composition in the range of about 10 mcg to 10 mg.

          The invention is also directed to a composition for administering to a person afflicted with diabetes mellitus comprising a therapeutic amount of an insulin sensitizer and a therapeutic amount of an orally ingestible anti-diabetic agent, the  
20       insulin sensitizer being selected from one or more of the group consisting of: BRL-49653 (Avandia), Rosiglitazone Maleate, Pioglitazone HCL (Actos), Troglitazone, MC 555, ALRT 268, LGD 1069, Metformin, Glucophage, Chromic Picolinate or V-411, a pharmaceutically acceptable vanadium salt or complex, Vanadyl Sulfate and Chromic Polynicotinate, and the anti-diabetic agent being selected from one or  
25       more of the group consisting of: an orally ingestible insulin, an injectible insulin, a sulfonylurea, a biguanide and an alpha-glucosidase inhibitor.

          The insulin sensitizer can be present in the composition in the range of about 10 mcg to 10 mg. The composition can include a pharmaceutically  
30       acceptable carrier. The biguanide can be glucophage.

#### DETAILED DESCRIPTION OF SPECIFIC EMBODIMENTS OF THE INVENTION

35           I have discovered unexpectedly that it is possible to overcome the problem of insufficient bloodstream levels of insulin typically associated with orally ingested insulin by incorporating an orally ingestible insulin sensitizer with an orally

- 10 -

ingestible insulin composition. While I do not wish to be bound adversely by any unsupported or invalid theories, the following description is offered as a possible explanation of why the combination of an orally ingestible insulin and an orally ingestible insulin sensitizer overcomes the problem caused by less than a therapeutic amount of insulin reaching the bloodstream when insulin is administered orally to a patient.

In typical oral ingestible insulin situations tested to date, insufficient levels of insulin reach the bloodstream of the diabetic person because most of the insulin is destroyed in the stomach and gut of the diabetic person. However, I have discovered that if an orally ingestible insulin sensitizer is added to the composition, and such sensitizers are not adversely affected by the strong digestive processes of the stomach and gut, the insulin sensitizer enables the lower levels of insulin that reach the bloodstream to be sufficient for purposes of enabling the cells of the body of the diabetic to function with the lower levels of insulin. In other words, it seems that the insulin sensitizer sensitizes the insulin insensitive cells of the body of the diabetic so that even low levels of insulin are able to attach or act to facilitate required glucose uptake by the cells. Hence there is sufficient glucose uptake by the cell to enable sufficient metabolism to take place.

20

My discovery is also applicable to insulin injection. When insulin is injected intravenously, in combination with an insulin sensitizer, less insulin is required to achieve the same therapeutic effect in the body. The insulin sensitizer increases the utilization of glucose at any given insulin level, so less insulin is required for an equal therapeutic result.

25

My discovery has application as well to other types of diabetes treatments, methods and drugs. When a sulfonylurea is hypoglycaemic used to stimulate insulin production and control diabetes mellitus, I have discovered that by including an insulin sensitizer with the sulfonylurea, less of the sulfonylurea is required to achieve the same therapeutic effect in the body. Since the amount of insulin sensitizer increases the utilization of glucose at any given insulin level, less insulin is required to be manufactured by the beta cells of the pancreas for an equal therapeutic result in the diabetic. As a result less of the sulfonylurea may be used and adverse side effects are reduced by the lower levels of sulfonylurea.

30  
35

When a biguanide hypoglycaemic is used to control diabetes mellitus, the amount of the biguanide required can be reduced, and yet the same blood glucose levels in the body can be achieved, when an insulin sensitizer is included with the biguanide. The insulin sensitizer increases the utilization of glucose at any given insulin level. As a biguanide reduces the amount of glucose delivered to the blood, reducing the amount of the biguanide will increase the glucose delivered to the blood which can be utilized by the body due to the addition of the insulin sensitizer. Also, adverse side effects are reduced.

My discovery is also applicable to alpha-glucosidase inhibitors. When an alpha-glucosidase inhibitor is used to control diabetes mellitus, less of the alpha-glucosidase inhibitor is required to achieve the same blood glucose levels in the body when an insulin sensitizer is included. Since an alpha-glucosidase inhibitor reduces the amount of glucose delivered to the blood, reducing the amount of the alpha-glucosidase inhibitor due to the addition of the insulin sensitizer will increase the level of glucose delivered to the blood which can be utilized by the body.

The therapeutic compositions according to the invention can be administered parentally, topically or internally, but preferably orally, since that is the easiest form of administration to a diabetic. The compositions according to the invention may be formulated in any suitable orally acceptable form by employing conventional formulation techniques and conventional pharmaceutically acceptable formulation ingredients. The subject compositions, for example, may be employed in nutritionally acceptable forms by incorporation of the compositions in a fibre supplement, a meal replacer, or a drink mix, or in pharmaceutically acceptable forms such as tablets or capsules in admixture with pharmaceutically acceptable carriers. The compositions according to the invention may also be used in combination with other pharmaceutically acceptable agents, for which the disclosed composition may be formulated in one unit with the other pharmaceutically effective agents, or in separate units administered at the same time or at separate times during a 24 hour period. The compositions according to the invention may be administered in single dosage form or in the form of sub-units several times a day.

- 12 -

ExampleG.B. - Case History

G.B. is a Type I diabetic who must normally inject insulin intravenously twice a day in order to control her Type I condition. G.B. volunteered one day to determine whether or not the addition of a small amount of an insulin sensitizer to her insulin injection would enable a lower level of insulin to be administered intravenously. At 8:30 a.m., G.B. injected intravenously her usual insulin dosage and at the same time ingested 120 mg of an oral insulin sensitizer known as V-411 (sold under the trade-mark DIAB II by Biotech Holdings Ltd.). By 11:00 a.m., the same morning, G.B. went into a hypoglycaemic state involving rapid heart beat, trembling, dizziness and other symptoms normally associated with hypoglycaemia, a condition which G.B. was very familiar with. Conventional treatment for hypoglycaemia is to quickly ingest sugar in order to raise the sugar levels in the bloodstream. Thus, G.B. immediately started sucking sugar cubes to endeavour to alleviate the hypoglycemic condition. However, it still took about an hour for her to stabilize her hypoglycaemic condition. A more rapid treatment would have been for G.B. to inject glucose (which she did not have) or go immediately to a hospital emergency ward for a clinically administered glucose injection.

It was clear from G.B.'s experience with the addition of the V-411 insulin sensitizer that the effects of the insulin sensitizer were very pronounced and thus a normal dosage of G.B.'s insulin resulted in a condition whereby the glucose in her blood was being utilized by the cells of her body at such a high rate of efficiency that she experienced a hypoglycaemic condition in her bloodstream. There was clearly a startling effect, and indeed perhaps a synergistic effect, created between the combination of insulin and the V-411 insulin sensitizer. It follows that much smaller dosages of insulin could have been used. Indeed, it was conceivable that such dosages could be of the same low level as experienced with orally administered insulin.

V-411 insulin sensitizer is known by the inventor to withstand the degradation effects of the gastric juices of the stomach and enzymatic action of the gut. Other insulin sensitizers can also withstand the effects of the digestive process. Because of the strong or synergistic effect involving the combination of insulin and the insulin sensitizer, it follows that the inclusion of an insulin sensitizer in

- 13 -

combination with an orally ingestible insulin should enable the orally ingestible insulin to work effectively in the treatment of diabetes mellitus. This is because the levels of insulin that must ultimately reach the bloodstream are greatly reduced, and such low levels are sufficient due to the effects of the insulin sensitizer.

## WHAT IS CLAIMED IS:

1. A method for the treatment of diabetes mellitus comprising administering to a person with diabetes mellitus a therapeutic amount of an insulin sensitiz-  
5     er with a therapeutic amount of an anti-diabetic agent.
2. A method as claimed in claim 1 comprising an insulin sensitiz-  
   er and an orally ingestible insulin.
- 10   3. A method as claimed in claim 1 comprising an insulin sensitiz-  
     er and an injectible insulin.
4. A method as claimed in claim 1 including a pharmaceutical carrier  
   with the therapeutically effective amount of the anti-diabetic agent and the insulin  
15     sensitizer.
5. A method as claimed in claim 1 wherein the anti-diabetic agent is one  
   or more substances selected from the group consisting of:
  - 20     (a) an orally ingestible insulin;
  - (b) an injectible insulin;
  - (c) a sulfonylurea;
  - (d) a biguanide; or
  - (e) an alpha-glucosidase inhibitor.
- 25   6. A method as claimed in claim 1 wherein the insulin sensitiz-  
     er is selected from one or more of the group consisting of: BRL-49653 (Avandia),  
     Rosiglitazone Maleate, Pioglitazone HCL (Actos), Troglitazone, MC 555, ALRT  
     268, LGD 1069, Metformin, Glucophage, Chromic Picolinate or V-411, a  
     pharmaceutically acceptable vanadium salt or complex, Vanadyl Sulfate and  
30     Chromic Polynicotinate, and the anti-diabetic agent is selected from one or more of  
     the group consisting of an orally ingestible insulin, an injectible insulin, a  
     sulfonylurea, a biguanide and an alpha-glucosidase inhibitor.
7. A composition for the treatment of diabetes mellitus in a mammal  
35     comprising:
  - (a) a therapeutic amount of an insulin sensitiz-  
     er; and
  - (b) a therapeutic amount of an anti-diabetic agent.

- 15 -

8. A composition as claimed in claim 7 wherein:

(a) the therapeutically effective amount of anti-diabetic agent is an orally ingestible insulin which is formulated to withstand degradation by passage through the stomach and upper intestine of the mammal so that a therapeutically effective level of insulin reaches the bloodstream of the mammal; and

5 (b) the therapeutically effective amount of the insulin sensitizer is one or more of an orally ingestible insulin sensitizer which withstands degradation by the stomach contents and upper intestinal tract of the mammal and reaches the bloodstream of the mammal and thereby sensitizes the cells of the mammal to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus  
10 reducing the orally ingested insulin required for a therapeutic dose.

9. A composition as claimed in claim 7 wherein:

(a) the therapeutically effective amount of anti-diabetic agent is an injected insulin; and

15 (b) the therapeutically effective amount of insulin sensitizer is one or more insulin sensitizers to sensitize the cells of the mammal so as to enhance insulin uptake and/or utilization of glucose by the cells of the mammal thus reducing the therapeutic dose required of injected insulin.

20

10. A composition as claimed in claim 7 including a pharmaceutically acceptable carrier.

11. A composition as claimed in claim 8 including a pharmaceutically acceptable carrier.

25

12. A composition as claimed in claim 8 wherein the insulin is synthetic insulin.

13. A composition as claimed in claim 9 wherein the insulin is synthetic insulin.

30

14. A composition as claimed in claim 8 wherein the orally ingestible insulin is present in the composition in the range of about 1 mcg to 100 mg and the insulin sensitizer is present in the composition in the range of about 10 mcg to 10  
35 mg.



- 16 -

15. A composition as claimed in claim 9 wherein the injected insulin is present in the composition in the range of about 1 mcg to 100 mg and the insulin sensitizer is present in the composition in the range of about 10 mcg to 10 mg.
- 5 16. Any composition as claimed in claim 8 wherein the insulin sensitizer is present in the composition in the range of about 10 mcg to 10 mg.
17. A composition as claimed in claim 9 wherein the insulin sensitizer is present in the composition in the range of about 10 mcg to 10 mg.
- 10 18. A composition as claimed in claim 7 wherein the anti-diabetic agent is one or more substances selected from the group consisting of:
- (a) an orally ingestible insulin;
  - (b) an injectible insulin;
  - 15 (c) a sulfonylurea;
  - (d) a biguanide; and
  - (e) an alpha-glucosidase inhibitor.
19. A composition as claimed in claim 18 wherein the anti-diabetic agent is orally ingestible insulin.
- 20 20. A composition as claimed in claim 18 wherein the anti-diabetic agent is injectible insulin.
- 25 21. A composition as claimed in claim 7 wherein the insulin sensitizer is selected from one or more of the group consisting of: BRL-49653 (Avandia), Rosiglitazone Maleate, Pioglitazone HCL (Actos), Troglitazone, MC 555, ALRT 268, LGD 1069, Metformin, Glucophage, Chromic Picolinate or V-411, a pharmaceutically acceptable vanadium salt or complex, Vanadyl Sulfate and
- 30 Chromic Polynicotinate, and the anti-diabetic agent is selected from one or more of the group consisting of an orally ingestible insulin, an injectible insulin, a sulfonylurea, a biguanide and an alpha-glucosidase inhibitor.
22. The use of a therapeutic amount of an insulin sensitizer and a
- 35 therapeutic amount of an orally ingestible anti-diabetic agent for a person afflicted with diabetes mellitus, the insulin sensitizer being selected from one or more of the group consisting of: BRL-49653, Pioglitazone HCL, Troglitazone, MC 555, ALRT

268, LGD 1069, Chromic Picolinate or V-411, Vanadyl Sulfate and Chromic Polynicotinate, and the anti-diabetic agent being selected from one or more of the group consisting of an orally ingestible insulin, an injectible insulin, a sulfonylurea, a biguanide and an alpha-glucosidase inhibitor.

5

23. The use as claimed in claim 22 wherein the insulin sensitizer is V-411.

10

24. The use as claimed in claim 22 wherein the anti-diabetic agent is an orally ingestible anti-diabetic agent.

25. The use as claimed in claim 22 wherein the anti-diabetic agent is an orally ingestible insulin.

15

26. The use as claimed in claim 22 wherein the insulin sensitizer is present in the composition in the range of about 10 mcg to 10 mg.

27. The use as claimed in claim 22 further comprising a pharmaceutically acceptable carrier.

20

28. The use as claimed in claim 22 wherein the biguanide is metformin or glucophage.

## INTERNATIONAL SEARCH REPORT

 International Application No.  
 PCT/CA 1152

## A. CLASSIFICATION OF SUBJECT MATTER

 IPC 7 A61K45/06 A61K38/28 A61K31/64 A61K31/44 A61K31/425  
 A61K33/24 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 861 666 A (TAKEDA CHEMICAL INDUSTRIES) 2 September 1998 (1998-09-02) claims 1-14 page 7, line 56 -page 8, line 57 page 9, line 45-55 page 10, line 7-22	1-22, 24-28
X	WO 98 57636 A (SMITHKLINE BEECHAM) 23 December 1998 (1998-12-23) claims 1,2,11,12 page 1, line 9-14 page 4, line 20-26 page 5, line 6-18	1-22, 24-27
	-/-	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

\*A\* document defining the general state of the art which is not considered to be of particular relevance

\*E\* earlier document but published on or after the international filing date

\*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

\*O\* document referring to an oral disclosure, use, exhibition or other means

\*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*Z\* document member of the same patent family

Date of the actual completion of the international search

25 June 2001

Date of mailing of the international search report

05/07/2001

Name and mailing address of the ISA

 European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Peeters, J

# INTERNATIONAL SEARCH REPORT

Inter Application No  
PCT/00/01152

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 00 27401 A (WARNER-LAMBERT) 18 May 2000 (2000-05-18)</p> <p>claims 1,3,4,6,7,9 page 6, line 21 -page 7, line 14 page 8, line 4-9</p>	<p>1,2,4-8, 10-12, 14,16, 18,19, 21,22, 24-27</p>
X	<p>WO 00 15211 A (AKESIS PHARMACEUTICALS) 23 March 2000 (2000-03-23)</p> <p>claims 1,4-6,8,10-12,16-18,20,46,47,53 page 52, line 19 -page 53, line 2</p>	<p>1-13, 18-22, 24,25, 27,28</p>
X	<p>A.FRITSCH: "Intensive insulin therapy combined with metformin in obese 2 diabetic patients" ACTA DIABEOLOGICA, vol. 37, no. 1, 2000, page 13-18 XP001009903 page 13 page 14 page 18</p>	<p>1,2,5-8, 12,18, 19,21, 22,24, 25,28</p>

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 1152

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 861666 A	02-09-1998	AU 723097 B	17-08-2000
		AU 5603496 A	09-01-1997
		CA 2179584 A	21-12-1996
		CN 1145783 A	26-03-1997
		CZ 9601811 A	15-01-1997
		EP 0749751 A	27-12-1996
		HU 9601698 A	28-05-1997
		JP 9067271 A	11-03-1997
		JP 10167986 A	23-06-1998
		NO 962606 A	23-12-1996
		NO 20004345 A	23-12-1996
		SK 79496 A	08-01-1997
		US 5965584 A	12-10-1999
		US 6150383 A	21-11-2000
		US 6169099 B	02-01-2001
		US 6133293 A	17-10-2000
		US 6166042 A	26-12-2000
		US 6214848 B	10-04-2001
		US 6166043 A	26-12-2000
		US 6150384 A	21-11-2000
		US 6172089 B	09-01-2001
		US 6172090 B	09-01-2001
		US 6121295 A	19-09-2000
		US 6156773 A	05-12-2000
		US 6174904 B	16-01-2001
		US 6121294 A	19-09-2000
		US 6225326 B	01-05-2001
		US 6080765 A	27-06-2000
		US 6133295 A	17-10-2000
		US 6103742 A	15-08-2000
		US 6169100 B	02-01-2001
		US 6211205 B	03-04-2001
		US 6232330 B	15-05-2001
		US 6218409 B	17-04-2001
		US 6239153 B	29-05-2001
		US 6211206 B	03-04-2001
		US 6211207 B	03-04-2001
		US 5952356 A	14-09-1999
WO 9857636 A	23-12-1998	AU 8216398 A	04-01-1999
		BG 104059 A	31-10-2000
		BR 9810444 A	05-09-2000
		CN 1260715 T	19-07-2000
		EP 0999837 A	17-05-2000
		HU 0003260 A	28-05-2001
		NO 996265 A	17-12-1999
		TR 9903095 T	21-08-2000
WO 0027401 A	18-05-2000	US 6011049 A	04-01-2000
		AU 5347399 A	29-05-2000
WO 0015211 A	23-03-2000	AU 6044699 A	03-04-2000

**THIS PAGE BLANK (USPTO)**